# Does orthodontic treatment have a permanent effect on tooth color? : A systematic review and meta-analysis

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Abstract: OBJECTIVES Aim of this systematic review was to assess the effect of orthodontic treatment with fixed appliances on the tooth color of patients. METHODS Nine databases were searched up to May 2017 for clinical cohort studies on the effect of fixed appliance treatment on tooth color. After elimination of duplicate studies, data extraction, and risk of bias assessment according to the Cochrane guidelines, random effects meta-analyses of mean differences (MD) or means and their 95% confidence intervals (CIs) were performed, followed by GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment of the quality of evidence. RESULTS Three nonrandomized and one randomized study with a total of 138 patients (46% male, 54% female) with average age of 15.7 years were included. Tooth color of treated patients was significantly altered during or after orthodontic treatment (4 studies; average of 3.2 ΔE units; 95% CI = 2.0-4.4 ΔE units), which was more than the variation among controls (1 study; MD = 1.9 ΔE units; 95% CI = 1.7-2.2 ΔE units). However, the quality of evidence was very low, due to the inclusion of nonrandomized studies, bias, and imprecision. Re-analysis of raw study data indicated that significant differences in clinically discernable treatment-induced color changes were seen between chemically and light-cured adhesives and among the various tooth categories. CONCLUSION Existing evidence of very low quality indicates that orthodontic treatment might be associated with alterations of tooth color, which are however not consistently clinically discernible. Treatment-induced color alterations might be dependent on bonding material and tooth type, but evidence supporting this is weak.

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**Title Page**

# Does orthodontic treatment have a permanent effect on tooth color? A systematic review and meta-analysis

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**Does orthodontic treatment have a permanent effect on tooth color? A systematic review and meta-analysis**


## Abstract

*Objectives* Aim of this systematic review was to assess the effect of orthodontic treatment with fixed appliances on the tooth color of human patients.

*Methods* Nine databases were searched up to May 2017 for clinical cohort studies on the effect of fixed appliance treatment on tooth color. After elimination of duplicate studies, data extraction, and risk of bias assessment according to the Cochrane guidelines, random effects meta-analyses of Mean Differences (MD) or means and their 95% confidence intervals (CIs) were performed, followed by GRADE assessment of the quality of evidence.

*Results* Three non-randomized and one randomized study with a total of 138 patients (46% male/ 54% female) with average age of 15.7 years were included. Tooth color of treated patients was significantly altered during or after orthodontic treatment (4 studies; average of 3.2 $\Delta E$ units; 95% CI=2.0-4.4 $\Delta E$ units), which was more than the variation among controls (1 study; MD=1.9 $\Delta E$ units; 95% CI=1.7-2.2 $\Delta E$ units). However, the quality of evidence was very low, due to the inclusion of non-randomized studies, bias, and imprecision. Re-analysis of raw study data indicated significant differences in clinically discernable treatment-induced color changes were seen between chemically- and light-cured adhesives and among the various tooth categories.

*Conclusion* Existing evidence of very low quality indicates that orthodontic treatment might be associated with alterations of tooth color, which are not however consistently clinically discernible. Treatment induced color alterations might be dependent on bonding material and tooth type, but evidence supporting this is weak.


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## MANUSCRIPT

## Introduction

Fixed appliances have become an integral part of contemporary orthodontic treatment, as they provide a secure hold on the teeth and enable efficient tooth movement in space. Fixed appliance treatment became more widespread with the introduction of the enamel etch technique [5] that enabled a secure fix of the orthodontic appliances bonded on the teeth and the development of more simplified appliances and techniques [29] that still provided precise biomechanical control of the teeth.

Although the ability of orthodontic appliances to therapeutically produced an acceptable outcome has been documented [33], several adverse effects to the soft and hard tissues of the oral cavity have also been reported, with the most prominent being gingival recessions [24], alveolar bone loss [4], periodontal attachment loss [34], root resorption [49], white spot lesions [15], and tooth discoloration [50].

Tooth color results from scattering of light through the tooth volume and is one of the main factors contributing to the pleasantness of the smile [26]. Tooth color seems to be mainly determined by dentin, with enamel playing a lesser role through scattering at wavelengths in the blue range [45]. Ultimately, tooth color can be influenced by a combination of intrinsic traits and extrinsic stains that may be present on the tooth surface or within the dental tissues [23], like stains promoted by smoking, drinking red wine, use of cationic agents such as chlorhexidine, or metal salts such as tin and iron [30, 48].

It has long been documented that the bonding and debonding procedures of orthodontic appliance on dental enamel can affect its color [13, 39]. This can be attributed to dissolution of enamel rods during acid etching [46], absorption of particles/substances from food, plaque, or degradation and corrosion products [11, 43], potentially discoloring [12] adhesive remnants on / in the dental tissues [37], and enamel injuries in terms of substance loss [2] or surface roughness [7, 12] during adhesive removal.

A previous systematic review on the subject reported that there is no strong evidence that orthodontic treatment with fixed appliances alters the original color of enamel [6]. However, that review included also in vitro studies, which might not reliably reflect the clinical situation [25]. Additionally, the last review covered studies published up to 2014, which means that it is possibly outdated [41]. Therefore, aim of the present systematic review was to critically assess evidence from longitudinal clinical studies on the effect of orthodontic treatment on tooth color and to answer the research question: Does orthodontic treatment have a permanent effect on tooth color of humans?

## Material and methods

### Protocol, eligibility criteria, and registration

The protocol for this review was made *a priori* based on the PRISMA-P statement [40], registered in PROSPERO (CRD42017064862), and all *post hoc* changes were appropriately noted. According to the PICOS schema, parallel or split-mouth randomized clinical trials and prospective non-randomized controlled or uncontrolled cohort studies on human patients assessing the effect of any kind of fixed orthodontic appliance on tooth color were included. Studies with potentially discoloring agents/treatment, studies not assessing tooth color, cross-sectional studies, animal studies, non-clinical studies, and non-relevant studies were excluded. This systematic review was conducted and reported according to Cochrane Handbook [19] and PRISMA statement [28], respectively.

### Information sources and literature search

A total of nine electronic databases were searched systematically by one author (SNP) without any limitations from inception up to May 16th, 2017 (Appendix 1). Two additional sources (Google Scholar and ISRCTN registry) were manually searched for additional studies by the same author. Authors of included studies were contacted for individual patient data (Appendix 2). No limitations concerning language, publication year or status were applied. The reference lists of the included trials and relevant reviews were manually searched as well.

### Study selection, data collection, and risk of bias in individual studies

Titles, abstracts, and full texts of studies identified from the literature search were screened by one author (RK) with a subsequent duplicate independent checking against the eligibility criteria by another author (SNP), while conflicts were resolved by the last author (TE). The same protocol was applied for the extraction of study characteristics (study design, setting, country, language, patient number, sex, age, malocclusion, appliances, treatment duration, oral hygiene measures, post-debond cleaning procedures, outcome measured, measurement unit, and timing) and numerical data using pre-determined and piloted extraction forms. Piloting of the forms was performed during the protocol stage until over 90% agreement was reached.

The risk of bias of the included randomized and non-randomized studies was assessed using Cochrane's risk of bias tool [19] and the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool [44], respectively.

## Data synthesis

The outcome for the meta-analysis was the overall change in tooth color (ΔE), as measured according to the CIE Lab system (Commision Internationale de l' Eclairage, L*, a*, b*). The CIE colour L* parameter corresponds to the value or degree of lightness in the Munsell system, whereas the a* and b* co-ordinates designate positions on red/ green (+a* = red, –a* = green) and yellow/blue (+b* = yellow, –b* = blue) axes. As the effects of orthodontic fixed appliance treatment is bound to be affected by many factors, including type of orthodontic appliances and adhesives, treatment duration, and patient-specific characteristics [3, 13, 50], a random-effects model was deemed appropriate to encompass this variability and calculate the average distribution of true effects among studies. The novel Paule-Mandel random-effects estimator was used instead of the DerSimonian and Laird one, based on recent guidance [47]. Mean Differences (MD) of treatment-induced changes between treated and untreated patients with their corresponding 95% Confidence Intervals (CI) were chosen as the primary outcome from controlled studies. Additionally, average treatment-induced changes among treated patients only were calculated as the secondary outcome for uncontrolled studies.

Absolute and relative between-trial heterogeneity was quantified with the $tau^2$ metric and the $I^2$ statistic, respectively. The latter is defined as the proportion of total variability in the results explained by heterogeneity, and not chance [17]. 95% CIs around all heterogeneity measures were calculated to quantify existing uncertainty. 95% predictive intervals were calculated for meta-analyses of three trials or more, to incorporate existing heterogeneity and provide a clinically-relevant range of possible effects for a future clinical setting [18]. Re-analysis of individidual patient data provided by the authors were performed with generalized linear regression that accounted for within-person clustering of teeth and setting a change of 3.7 ΔE units as a cut-off for clinically perceivable color change [22]. All analyses were run in Stata SE 14.0 (StataCorp, College Station, TX) by one author (SNP). A two-tailed P-value of 0.05 was considered significant for hypothesis-testing, except for a 0.10 used for the test of heterogeneity and reporting biases.

## Additional analyses and risk of bias across studies

Possible sources of heterogeneity were planned in the protocol to be sought through mixed-effects subgroup analyses and random-effects meta-regression for meta-analyses of ≥ fives studies. Eventually, subgroups analyses were only descriptively given, but not formally conducted, as less than five studies existed. The same goes for the assessment of reporting biases and publication bias that couldn't be formally assessed as <10 studies were finally included. The overall quality of evidence (confidence in effect estimates) for each outcome was rated using the GRADE approach [16]. The minimal clinical important, large, and very large effects were to augment the produced forest plots with contours of effect magnitude [32]. Robustness of the results were planned to be checked through sensitivity analysis controlling for of bias originating from biased study designs, inconsistency, or reporting biases.

## Results

### Study selection

The literature search yielded a total of 427 hits (Fig. 1), 32 of which proceeded to full text assessment after eliminating duplicates and ineligible studies by title or abstract (Appendix 3). Finally, a total of four papers were identified as eligible for inclusion in the present systematic review, which pertained to four unique clinical studies published in English between 2010 and 2015 were included. Apart from data from published reports, we attempted to procure individual patient data from all included studies to reanalyze, however only one answered and provided raw data [25].

### Study characteristics

The descriptive characteristics of the four included studies can be seen in Tables 1-2. From these, one was a randomized trial comparing self-etching and conventional adhesives, one was a prospective controlled cohort study comparing treated and untreated patients, one was a prospective uncontrolled cohort study comparing light-cured to chemically-cured adhesives, and the last was a prospective uncontrolled cohort study of conventional appliances. The included studies were conducted in university clinics in Greece, Iraq, Jordan, and Turkey. Overall, 138 patients were included with a mean age of 15.7 years (from the 3 studies reporting mean age) and with 46.4% patients being male (from the 4 studies reporting sex). All studies assessed color changes of anterior/posterior teeth at either tooth or patient level.

### Risk of bias within studies

The risk of bias assessment is reported in Table 3 for the identified studies. Both the one randomized and all three non-randomized studies were found to be in high or serious risk of bias. The most problematic issues were confounding, lack of blinding, and selective reporting or missing data.

**Results of individual studies and data synthesis**

Most of the analyses were based on the data included in the published report. The only exception was the study of Karamouzos et al. [25], where the authors provided raw data for re-analysis (Appendix 4-7). The results indicated that orthodontic treatment lead to an average change by about 2.8 ΔE units (Appendix 4). Additionally, teeth bonded with chemically-cured composite were more heavily discolored than those bonded with light cured composite (difference of 0.4 ΔE units; $P<0.001$; Appendix 5). Also, considerable variance was found among teeth, with canines being the least discolored, followed by central incisors, 1st premolars, and finally lateral incisors, which were the most discolored teeth (Appendix 5). No difference was found between upper versus lower teeth or right versus left teeth. As far as clinical relevance is concerned, 13% of all treated teeth had color changes that could be clinically discernible (change ≥ 3.7 ΔE units). Teeth bonded with chemically-cured composite were in 158% higher risk of clinically-relevant discoloration than those bonded with light-cured composite (Appendix 6). Finally, lateral incisors had 197% higher risk of clinically-relevant discoloration compared to canines (Appendix 6).

As far as analysis of the primary outcome from controlled data is concerned, evidence from one study indicated that orthodontic treatment was associated with an overall statistically significant tooth color change 4-9 months into treatment by 1.9 ΔE units (95% CI=1.7 to 2.2) compared to untreated patients (Table 4). However, the quality of evidence according to the GRADE approach was judged as very low, due to the non-randomized nature of the study, bias, and imprecision.

Meta-analysis of the secondary outcome of treatment-induced color changes of the teeth of treated patients are given in Table 5. Meta-analysis of four studies and 946 teeth indicated that the color of orthodontically treated teeth changed on average by 3.2 ΔE units (95 CI=2.0-4.4) during or after orthodontic treatment compared to the pre-treatment color. However, extreme absolute or relative heterogeneity was observed, which led to a very imprecise prediction interval of -3.2 to 10.1 ΔE units that was inconclusive.

Additional analyses

As the primary outcome from controlled data was reported only by a single non-randomized study, sensitivity analyses could be performed only for the secondary outcome of uncontrolled data. Sensitivity analyses either to alleviate the extreme heterogeneity seen or to omit the potentially biased non-randomized study designs led to similar results, indicating that orthodontic treatment was associated with an average tooth color change by about 2.8-2.9 ΔE units, which was slightly lower than the original analysis (Table 6). Subgroup analyses were planned a priori but could not eventually be conducted formally. Evidence of different color change pattern might be seen between chemically- and light-cured resins (as stated before) and according to the vertical thirds of each crown surface (incisal, middle, and apical third), but formal analyses are needed to confirm or refute them.

## Discussion

The present systematic review summarized evidence from clinical controlled and uncontrolled studies on the effect of orthodontic treatment on tooth color changes. The results of the four identified studies, including 946 teeth, indicated that orthodontic treatment with fixed appliances might have a significant effect on tooth color, although this is not always clinically discernable. After active treatment, the average tooth color becomes darker and shifts into more red and especially yellow color ranges [25, 27]. Possible explanations for these changes include enamel crystal dissipation during etching [36], resin tag penetration in enamel [13], development of white spot lesions [31], absorption of food colorants [21] or corrosion products [20], enamel morphology alteration by debonding and adhesive removal [51]. Additionally, re-analysis of raw data from a single study [25] indicated that about 13% of all bonded teeth present clinically discernable color changes, but this is more prevalent on patient level, where only 20% of patients have no clinically discernable discolorations and the rest have at least one tooth with changed color (Appendix 4).

Considerable differences were seen in the treatment-induced color change among the various bonded teeth with canines being the least affected, followed by central incisors, 1$^{st}$ premolars, and ultimately lateral incisors, which were most affected (Appendix 5-6) [25]. Another study reported no effect of tooth type on treatment-induced color change [1], but raw data were not available for re-analysis.

There are many factors that might possibly influence the effect of orthodontic treatment on tooth color, including among others patient characteristics, etching/bonding protocol, characteristics of the orthodontic appliance, treatment duration, post-debond cleaning protocol, oral hygiene during treatment, and the patient's dietary preferences. However, no evidence currently exists about theses and well-designed clinical studies with adequate sample and appropriate analysis are needed to investigate these and minimize the adverse effects of orthodontics on tooth color.

Limited evidence indicated that chemically-cured composite resins used to bond the orthodontic appliances lead to significantly more discoloration to a clinically relevant point than light-cured composite resins (Appendix 5-6) [25]. This might be attributed to chemical differences between the two resins [10, 12, 14] like filler content and polymerization conversion, which might affect their color stability. Another study reported no color differences between teeth bonded with self-etching or conventional etch & prime protocol [1]. This was attributed to the similarity between the two protocols of the etching pattern at the uppermost enamel layer, which discolors first, independently of penetration depth [8]. However, caution is warranted by the interpretation of these data, as evidence was of poor quality, due to the non-randomized study design and its inherent bias. Further evidence from well-designed randomized trials is needed to confirm or refute this finding.

Although the present systematic review has several strengths including a priori registration [42], extensive literature search, inclusion of individual patient data, and appropriate methods to risk of bias assessment [19, 44], data synthesis [47], and critical appraisal [16], several limitations also existed. First of all, only a handful of studies could be eventually included in the review, which affects the results' robustness and precluded the conduct of many planned analyses (Appendix 7). Additionally, three out of the four included studies were non-randomized, which means their conclusions might be potentially biased [35]. Finally, although color assessments with the CIE Lab protocol are more objective and consistent than subjective visual inspections of color, it still is prone to systematic and random errors [9, 38].

The results of the present study are applicable to adolescent and post-adolescent patients that receive fixed appliance treatment in orthodontic university clinics. The results might be less generalizable to pre-adolescent or older adult patients or patients that seek treatment in other clinical settings.

## Conclusion

The present systematic review of in vivo clinical evidence indicates that fixed appliance treatment seems associated with statistically significant alteration of tooth color. These color changes are not always visible clinically and considerable difference are seen according to the bonding material and the various teeth. However, existing evidence is limited and based mainly on potentially flawed study designs and therefore additional studies are needed in order to robustly assess the effect of orthodontic treatment on tooth color and to find ways to minimize this.

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## TABLES

**Tab. 1** Patient demographics of the included studies

| Study ID | Design; setting; country; language | Patients (M/F); Age in years* | Malocclusion; Tx plan | Tx duration* | Appliances; Ligs | OH status; OH measures | Post-debond cleaning |
|---|---|---|---|---|---|---|---|
| Al Maaitah 2013 | $RCT_{sm}$; Uni; JOR; EN | EG1/EG2: 34 (13/21) 18.6 | EG1/EG2: NR; NR | 12.0-15.0 mos | SS BRs; NR<br>EG1: SEP<br>EG2: conv primer | Good OH; OH instructions | Spiral 12-fluted tungsten carbide bur (low-speed) |
| Corekci 2015 | $pNRS_{sm/par}$; Uni; TUR; EN | EG1-4: 22 (11/11); 14.4<br>CG: 22 (10/12); 15.1 | EG1-4: crowding<4 mm; NR<br>CG: no crowding; NR | EG1-4: 4.3 mos<br>CG: 8.5 mos | SS BRs; SS Ligs<br>EG1-4: 4 different ADHs | Good OH; OH assessment/ motivation | Carbide bur (high- then low-speed); sof-lex polishing discs |
| Karamouzos 2010 | $pNRS_{sm}$; Uni; GR; EN | EG1-2: 26 (13/13); 13.6 | EG1-2: crowding<4 mm NR; NR | 18.0-26.0 mos | SS BRs<br>EG1: chem-cured ADH<br>EG2: light-cured ADH | Good OH; OH assessment and motivation at every appointment | Carbide bur (low-speed) |
| Al-Laban 2015 | pNRS; Uni; IRQ; EN | EG: 34 (17/17); 18.0-40.0 | NR; NR | NR | SS BRs | Good OH; OH instructions; bad-OH patients excluded | 12 fluted tungsten carbide bur (low-speed); extra fine sof-lex polishing discs |

*when one number is given, this pertains to the mean; if mean is not reported, then the range is given as two values.
BR, bracket; CG, control (untreated) group; Conv, conventional; ADH, adhesive; EG, experimental (treated) group; Ligs, ligatures; NR, not reported; OH, oral hygiene; par, parallel design; pNRS, prospective non-randomized study; RCT, randomized clinical trial; $RCT_{sm}$, split mouth randomized clinical trial; SEP, self-etching primer; sm, split mouth (or within-patient group allocation) design; SS, stainless steel; Tx, treatment; uni, university.

**Tab. 2** Outcome characteristics of the included studies

| Study | Outcome | Measured teeth | Measurement unit | Outcome timing |
|---|---|---|---|---|
| Al Maaitah 2013 | CIE L*a*b* | Max/Mand 3-3 | Tooth | ▪ Pre-bond<br>▪ 1 wk post-debond |
| Corekci 2015 | CIE L*a*b* | 42, 41, 31, 32 | Tooth | ▪ Pre-bond<br>▪ 4.3-8.5 mos after bond |
| Karamouzos 2010 | CIE L*a*b* | Max/Mand 4-4 | Tooth | ▪ Pre-bond<br>▪ Post-debond |
| Al-Laban 2015 | CIE L*a*b* | 3-3 | Patient | ▪ Pre-bond<br>▪ Post-debond |

CIE L*a*b*, color space as specified by the International Commission on Illumination; Mand, mandibular; Max, maxillary; mo, month; wk, week.

**Tab. 3** Risk of bias assessment of randomized and non-randomized identified studies

| Bias domain for RCTs | Al-Maaitah 2013 | | Bias domain for non-RCTs | Al Laban 2015 | Corekci 2015 | Karamouzos 2010 |
|---|---|---|---|---|---|---|
| Sequence generation | Unclear | | Confounding | Serious | Serious | Moderate |
| Allocation concealment | Low | | Selection of participants | Low | Low | Moderate |
| Blinding of participants/ personnel | Unclear | | Classification of interventions | Low | Low | Low |
| Blinding of outcome assessors | High | | Deviations from intended interventions | Low | Low | Low |
| Incomplete outcome data | High | | Missing data | Serious | Serious | Serious |
| Selective outcome reporting | High | | Measurement of outcomes | Moderate | Low | Moderate |
| Other sources of bias | Unclear | | Selection of reported results | Moderate | Moderate | Moderate |
| Overall | High | | Overall | Serious | Serious | Serious |

RCT, randomized clinical trial.

**Tab. 4** Results of the single identified controlled clinical study comparing treated and untreated patients

| Study (teeth) | Comparison | Timing | Outcome | Mean Difference | 95% Confidence Interval | P |
|---|---|---|---|---|---|---|
| 1 (176) | Treatment vs Control | 4.3-8.5 months after bonding | ΔE | 1.94 | 1.71,2.18 | <0.001 |

**Tab. 5** Summary of findings table according to the GRADE approach based on the single identified controlled clinical study comparing treated and untreated patients

| | Anticipated absolute effects | | | | |
|---|---|---|---|---|---|
| **Outcome**<br>Trials (patients) – follow-up | **Control*** | **Tx** | **Difference Tx-control (95% CI)** | **Quality of the evidence (GRADE)**[a] | **What happens to treated teeth** |
| Change in *E* (total color difference)<br>1 trial (176 teeth) – 4-9 mos | $\Delta E$ is increased by 0.29 | - | 1.94 increase (1.71 to 2.18 increase) | ⊕○○○ very low[a,b]<br>due to bias, imprecision | May lead to increase in total color difference $\Delta E$. |

Effects of fixed appliance treatment on tooth color.
Patient or population: pre- or post-adolescence non-adult patients attending an orthodontic university clinic.
Settings: university clinics (Turkey).
[*] Reponse in the untreated group of the one included controlled clinical study.
[a] Starts from "low", due to the inclusion of non-randomized studies. Downgraded further by one point due to serious limitations (high risk of bias).
[b] Downgraded by one due to imprecision originating from the inclusion of a small sample size.
Abbreviations
CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; Tx, treatment.

**Tab. 6** Meta-analysis of all 4 identified controlled or uncontrolled clinical studies on tooth color changes (before & after treatment) of treated patient

| **Outcome** | **Studies (teeth)** | **Tx change** | **95% CI** | **P** | **$I^2$ (95% CI)** | **$t^2$ (95% CI)** | **95% prediction** |
|---|---|---|---|---|---|---|---|
| *Original analysis* | | | | | | | |
| $\Delta E$ | 4 (946) | 3.21 | 2.03,4.38 | <0.001 | 100% (100%-100%) | 1.42 (0.44-20.0) | -3.63,10.05 |
| *Sensitivity analysis (*Two studies omitted to alleviate extreme heterogeneity*)* | | | | | | | |
| $\Delta E$ | 2* (824) | 2.84 | 2.80,2.88 | <0.001 | 32% (0-100%) | 0 (0-1.27) | NA |
| *Sensitivity analysis (three non-randomized studies* omitted*)* | | | | | | | |
| $\Delta E$ | 1 (408) | 2.85 | 2.83,2.87 | <0.001 | NA | NA | NA |

CI, confidence interval; NA, non-applicable; Tx, treatment.

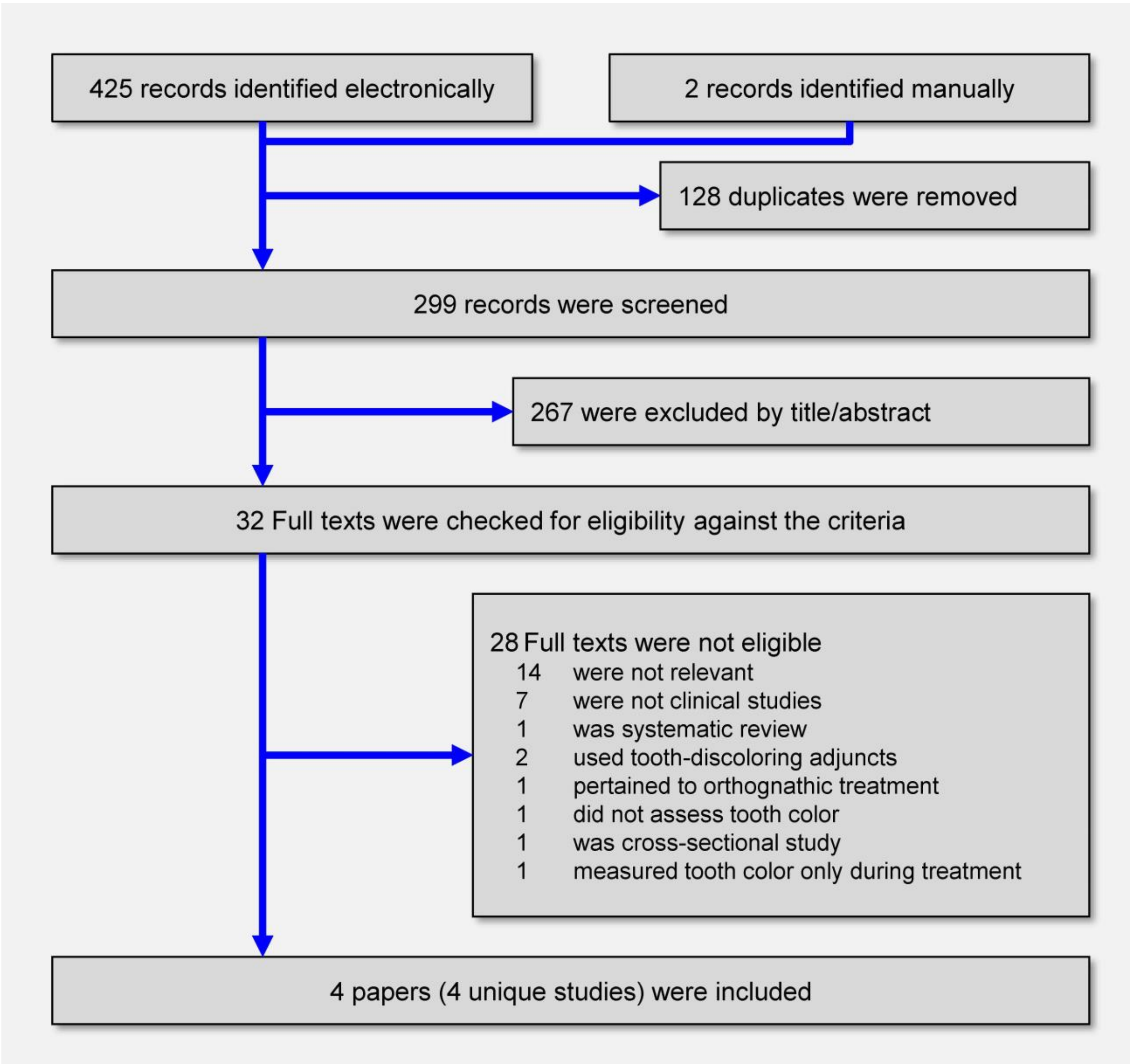
**Tab. 7** Explorative assessment of subgroup differences in total color change Δ*E* according to identified controlled or uncontrolled clinical studies

| **Studies (teeth)** | **Subgroup** | **Tx Change** | **95% CI** | **$P_{SG}$** |
|---|---|---|---|---|
| 1 (208) | Maxillary teeth | 2.75 | 2.63,2.87 | NA |
| 1 (208) | Mandibular teeth | 2.86 | 2.74,2.98 | |
| | | | | |
| 1 (17) | Female patients | 4.30 | 3.77,4.83 | NA |
| 1 (17) | Male patients | 4.14 | 3.69,4.59 | |
| | | | | |
| 1 (208) | Anterior teeth (incisors) | 2.82 | 2.70,2.94 | NA |
| 1 (208) | Posterior teeth (canine and premolar) | 2.80 | 2.70,2.90 | |
| | | | | |
| 1 (208) | Light-cured adhesive | 2.60 | 2.50,2.70 | NA |
| 1 (208) | Chemically-cured adhesive | 3.00 | 2.88,3.12 | |
| | | | | |
| 1 (17) | Incisal tooth third | 3.64 | 3.29,3.99 | NA |
| 1 (17) | Middle tooth third | 4.96 | 4.65,5.27 | |
| 1 (17) | Gingival tooth third | 4.05 | 3.68,4.42 | |

CI, confidence interval; NA, non-applicable; $P_{SG}$, p value for subgroup differences; Tx, treatment.

**Figure Captions**

**Fig. 1.** PRISMA flow diagram for the identification and selection of studies for this systematic review



## Does orthodontic treatment have a permanent effect on tooth color? A systematic review and meta-analysis

**Appendix 1**. Search strategy for each database with the corresponding hits (last search 16.5.2017)

| Nr | Database | Search | Limit | Hits |
|---|---|---|---|---|
| 1 | PubMed | (orthodon* OR malocclusion) AND (treatment OR therapy OR brace* OR bracket* OR "fixed appliance") AND (tooth OR teeth) AND (color* OR colour* OR discolor* OR discolour*) | (Human)(Clinical Study; Clinical Trial; Clinical Trial, Phase I-IV; Comparative Study; Controlled Clinical Trial; Multicenter Study; Observational Study; Pragmatic Clinical Trial; Randomized Controlled Trial) | 110 |
| 2 | CDSR | Same | - | 0 |
| 3 | CENTRAL | Same | - | 37 |
| 4 | DARE | Same | - | 0 |
| 5 | Embase | Same | - | 76 |
| 6 | VHL | Same | Humans | 47 |
| 7 | Scopus | Same | (Dentistry)(Human; Humans)(Controlled Study; Randomized Controlled Trial; Controlled Clinical Trial; Clinical Trial) | 42 |
| 8 | WoK | (orthodon* OR malocclusion) AND (treatment OR therapy OR brace* OR bracket* OR "fixed appliance") AND (tooth OR teeth) AND (color* OR colour* OR discolor* OR discolour*) | DENTISTRY ORAL SURGERY MEDICINE | 110 |
| 9 | ClinicalTrials | orthodontic AND (color OR colour OR discoloration OR discolouration) | | 3 |
| | **SUM (with overlap)** | | | **425** |
| | **SUM (without overlap)** | | | **297** |

**Appendix 2**. Authors contacted for individual patient data.

| Nr | Paper | |
|---|---|---|
| 1 | Al Maaitah EF, Abu Omar AA, Al-Khateeb SN. Effect of fixed orthodontic appliances bonded with different etching techniques on tooth color: a prospective clinical study. Am J Orthod Dentofacial Orthop. 2013;144(1):43-9. | E-mailed October 23rd; awaiting response. |
| 2 | Al-Laban YRA. Comparison of enamel color alteration between bonded and free unbonded surfaces of maxillary anterior teeth after fixed orthodontic therapy : A Prospective Clinical Study. J Baghdad College Dentistry 2015;27:174-178. | E-mail could not be found |
| 3 | Corekci B, Toy E, Ozturk F, Malkoc S, Ozturk B. Effects of contemporary orthodontic composites on tooth color following short-term fixed orthodontic treatment: a controlled clinical study. Turk J Med Sci. 2015;45(6):1421-8. | E-mailed October 23rd; awaiting response. |
| 4 | Karamouzos A, Athanasiou AE, Papadopoulos MA, Kolokithas G. Tooth-color assessment after orthodontic treatment: a prospective clinical trial. Am J Orthod Dentofacial Orthop. 2010;138(5):537.e1-8; discussion -9. | E-mailed October 23rd; responded and provided individual patient raw data. |

**Appendix 3**. List of all identified studies together with their selection status.

| Nr | Paper | Status |
|---|---|---|
| 1 | Agrawal A, Shigli A. Comparison of six different methods of cleaning and preparing occlusal fissure surface before placement of pit and fissure sealant: an in vitro study. J Ind Soc Pedodont Prev Dent 2012;30(1):51-5. | Exclusion by title |
| 2 | Ahrari F, Akbari M, Mohammadpour S, Forghani M. The efficacy of laser-assisted in-office bleaching and home bleaching on sound and demineralized enamel. Laser Therapy. 2015;24(4):257-64. | Exclusion by title |
| 3 | Akin M, Baka ZM, Ileri Z, Basciftci FA. Can demineralized enamel surfaces be bonded safely? Acta Odontologica Scandinavica. 2014;72(4):283-9. | Exclusion by title |
| 4 | Akyalcin S, Alexander SP, Silva RM, English JD. Evaluation of three-dimensional root surface changes and resorption following rapid maxillary expansion: a cone beam computed tomography investigation. Orthod Craniofac Res. 2015;18 Suppl 1:117-26. | Exclusion by title |
| 5 | Albino LGB, Gradinar O, Bertholdo G, Cruz M. Otimizando a composição do sorriso com resina composta direta. Clín int j braz dent. 2013;9(3):262-70. | Exclusion by title |
| 6 | Alkilzy M, Berndt C, Meller C, Schidlowski M, Splieth C. Sealing of proximal surfaces with polyurethane tape: a two-year clinical and radiographic feasibility study. J Adhes Dent. 2009;11(2):91-4. | Exclusion by title |
| 7 | Almeida FT, Leite AF, De Souza Figueiredo PT, Melo NS, Sousa JB, Almeida R, et al. Dento-osseous anomalies associated to familial adenomatous polyposis mimicking florid cemento-osseous dysplasia. Journal of Cranio-Maxillofacial Surgery. 2012;40(8):e498-e502. | Exclusion by title |
| 8 | Almeida RC, Cevidanes LHS, Carvalho FAR, Motta AT, Almeida MAO, Styner M, et al. Soft tissue response to mandibular advancement using 3D CBCT scanning. International Journal of Oral and Maxillofacial Surgery. 2011;40(4):353-9. | Exclusion by title |
| 9 | Aloysius AP, Vijayalakshmi D, Deepika, Soundararajan NK, Manohar VN, Khan N. Comparative evaluation of frictional properties, load deflection rate and surface characteristics of different coloured TMA archwires - An invitro study. Journal of Clinical and Diagnostic Research. 2015;9(12):ZC26-ZC9. | Exclusion by title |
| 10 | Alves dos Santos MP, Luiz RR, Maia LC. Randomised trial of resin-based restorations in Class I and Class II beveled preparations in primary molars: 48-month results. J Dent. 2010;38(6):451-9. | Exclusion by title |
| 11 | Andersson L, Emami-Kristiansen Z, Hogstrom J. Single-tooth implant treatment in the anterior region of the maxilla for treatment of tooth loss after trauma: a retrospective clinical and interview study. Dental Traumatology. 2003;19(3):126-31. | Exclusion by title |
| 12 | Andrade MR, Salazar SL, de Sa LF, Portela M, Ferreira-Pereira A, Soares RM, et al. Role of saliva in the caries experience and calculus formation of young patients undergoing hemodialysis. Clin Oral Investig. 2015;19(8):1973-80. | Exclusion by title |
| 13 | Argueta-Figueroa L, Scougall-Vilchis RJ, Morales-Luckie RA, Olea-Mejia OF. An evaluation of the antibacterial properties and shear bond strength of copper nanoparticles as a nanofiller in orthodontic adhesive. Aust Orthod J. 2015;31(1):42-8. | Exclusion by title |
| 14 | Artun J, Grobety D. Periodontal status of mandibular incisors after pronounced orthodontic advancement during adolescence: A follow-up evaluation. Am J Orthod Dentofacial Orthop 2001;119(1):2-10. | Exclusion by title |
| 15 | Associação Brasileira de Cirurgiões-DentisasPedrazzi H, s.afSantos CRd, Associação Odontológica de Ribeirão PretoTakeuchi CYG, Universidade Estadual PaulistaAndrade MFd. Reabilitação estética do sorriso por meio do sistema cerâmico dissilicato de lítio – relato de caso. Full dent sci. 2015;6(21):112-7. | Exclusion by title |
| 16 | Bacci C, Lucchiari N, Valente M, Della Barbera M, Frigo AC, Berengo M. Intra-oral bone harvesting: two methods compared using histological and histomorphometric assessments. Clin Oral Implants Res. 2011;22(6):600-5. | Exclusion by title |
| 17 | Baek J, Wilder-Smith P, Na J, Lee BH. Periodontal tissue changes can be imaged during orthodontic tooth movement. Lasers in Surgery and Medicine. 2010;42:49-50. | Exclusion by title |
| 18 | Bakor SF, Pereira JCM, Frascino S, Ladalardo TCCGP, Pignatari SSN, Weckx LLM. Desmineralização dentária de pacientes respiradores orais submetidos à expansão maxilar. Braz J Otorhinolaryngol. 2010;76(6):709-12. | Exclusion by title |
| 19 | Ballard RW, Hagan JL, Phaup AN, Sarkar N, Townsend JA, Armbruster PC. Evaluation of 3 commercially available materials for resolution of white spot lesions. Am J Orthod Dentofacial Orthop. 2013;143(4 Suppl):S78-84. | Exclusion by title |
| 20 | Bartoňová M, Dostálová T, Peterka M, Kozák J, Müllerová Ž. Long-term stability of prosthetic treatment of oronasal and oroantral communications. Acta Chirurgiae Plasticae. 2005;47(3):85-91. | Exclusion by title |
| 21 | Batista EL, Jr., Batista FC, Novaes AB, Jr. Management of soft tissue ridge deformities with acellular dermal matrix. Clinical approach and outcome after 6 months of treatment. J Periodontol. 2001;72(2):265-73. | Exclusion by title |
| 22 | Batson ER, Cooper LF, Duqum I, Mendonça G. Clinical outcomes of three different crown systems with CAD/CAM technology. Journal of Prosthetic Dentistry. 2014;112(4):770-7. | Exclusion by title |
| 23 | Baty DL, Volz JE, von Fraunhofer JA. Force delivery properties of colored elastomeric modules. Am J Orthod Dentofacial Orthop. 1994;106(1):40-6. | Exclusion by title |
| 24 | Bauss O, Schafer W, Sadat-Khonsari R, Knosel M. Influence of orthodontic extrusion on pulpal vitality of traumatized maxillary incisors. J Endod. 2010;36(2):203-7. | Exclusion by title |
| 25 | Bazargani F, Jacobson S, Lennartsson B. A comparative evaluation of lingual retainer failure bonded with or without liquid resin: A randomized clinical study with 2-year follow-up. Angle Orthodontist. 2012;82(1):84-7. | Exclusion by title |
| 26 | Becker A, Chaushu S. Long-term follow-up of severely resorbed maxillary incisors after resolution of an etiologically associated impacted canine. Am J Orthod Dentofacial Orthop 2005;127(6):650-4. | Exclusion by title |
| 27 | Benson PE, Shah AA, Campbell IF. Fluoridated elastomers: effect on disclosed plaque. J Orthod. 2004;31(1):41-6. | Exclusion by title |
| 28 | Bharti R, Chandra A, Tikku AP, Prasad V, Shakya VK, Singhal R. Management of mucosal fenestration with external root resorption by multidisciplinary approach. BMJ Case Reports. 2014;2014. | Exclusion by title |
| 29 | Bidra AS, Uribe F. Successful Bleaching of Teeth with Dentinogenesis Imperfecta Discoloration: A Case Report. Journal of Esthetic and Restorative Dentistry. 2011;23(1):3-10. | Exclusion by title |
| 30 | Bjerklin K, Guitirokh CH. Maxillary incisor root resorption induced by ectopic canines. Angle Orthod. 2011;81(5):800-6. | Exclusion by title |
| 31 | Blasco Sansano R, Castellar Ponce MD, Llorca Salort N, Valero Rosique J, García Espinosa S. Estudio sobre los factores de riesgo de caries y evaluación de un test indicador del pH y revelado de la placa y la capacidad tampón de la saliva. Pediatr aten prim. 2009;11(41):33-47. | Exclusion by title |
| 32 | Boeira GF, Salas MMS, Araújo DC, Masotti AS, Correa MB, Demarco FF. Factors influencing dental appearance satisfaction in adolescents: a cross-sectional study conducted in Southern Brazil. Braz j oral sci. 2016;15(1):8-15. | Exclusion by title |
| 33 | Borges AB, Caneppele TMF, Masterson D, Maia LC. Is resin infiltration an effective esthetic treatment for enamel development defects and white spot lesions? A systematic review. J Dent 2017;56:11-8. | Exclusion by title |
| 34 | Borges CM, Peres MA, Peres KG. Associação entre presença de oclusopatias e insatisfação com a aparência dos dentes e gengivas: estudo com adolescentes brasileiros. Rev Bras Epidemiol. 2010;13(4):713-23. | Exclusion by title |
| 35 | Borzabadi-Farahani A, Borzabadi-Farahani A. The association between orthodontic treatment need and maxillary incisor trauma, a retrospective clinical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(6):e75-80. | Exclusion by title |

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|---|---|---|
| 36 | Bowen RL, Rupp NW, Eichmiller FC, Stanley HR. Clinical biocompatibility of an experimental dentine-enamel adhesive for composites. Int Dent J. 1989;39(4):247-52. | Exclusion by title |
| 37 | Boyd RL, Hollander BN, Eakle WS. Comparison of a subgingivally placed cannula oral irrigator tip with a supragingivally placed standard irrigator tip. J Clin Periodontol. 1992;19(5):340-4. | Exclusion by title |
| 38 | Boyd RL. Long-term evaluation of a SnF2 gel for control of gingivitis and decalcification in adolescent orthodontic patients. Int Dent J. 1994;44(1 Suppl 1):119-30. | Exclusion by title |
| 39 | Brauchli LM, Senn C, Ball J, Wichelhaus A. Force levels of 23 nickel-titanium open-coil springs in compression testing. Am J Orthod Dentofacial Orthop 2011;139(5):601-5. | Exclusion by title |
| 40 | Brazilian Dental J, Araujo JFd, Braga EMF, Loretto SC, Souza PdARSe, Barros TAdF, et al. One-Year Evaluation of a Simplified Ethanol-Wet Bonding Technique: A Randomized Clinical Trial. Braz Dent J. 2013;24(3):267-72. | Exclusion by title |
| 41 | Brightman LJ, Terezhalmy GT, Greenwell H, Jacobs M, Enlow DH. The effects of a 0.12% chlorhexidine gluconate mouthrinse on orthodontic patients aged 11 through 17 with established gingivitis. Am J Orthod Dentofacial Orthop. 1991;100(4):324-9. | Exclusion by title |
| 42 | Brough E, Donaldson AN, Naini FB. Canine substitution for missing maxillary lateral incisors: the influence of canine morphology, size, and shade on perceptions of smile attractiveness. Am J Orthod Dentofacial Orthop. 2010;138(6):705.e1-9. | Exclusion by title |
| 43 | Buckley JG, Jones ML, Hill M, Sugar AW. An evaluation of the changes in maxillary pulpal blood flow associated with orthognathic surgery. Br J Orthod. 1999;26(1):39-45. | Exclusion by title |
| 44 | Carrillo Baracaldo JS, Álvarez Quesada C, Calatayud Sierra J. Trabajo en equipo en Odontología: la comunicación con el laboratorio dental como clave de éxito clínico. A propósito de un caso clínico de tratamiento multidisciplinar. Cient dent (Ed impr). 2006;3(2):129-36. | Exclusion by title |
| 45 | Carrillo Baracaldo JS, Álvarez Quesada MdC, Costa Ferrer F. Utilización de nuevos equipamientos en Odontología. A propósito de un caso clínico de gingivectomía con láser de diodo. Cient dent (Ed impr). 2004;1(1):39-43. | Exclusion by title |
| 46 | Chalub LLFH, Martins CC, Ferreira RC, Vargas AMD. Functional dentition in Brazilian adults: An investigation of social determinants of health (SDH) using a multilevel approach. PLoS ONE. 2016;11(2). | Exclusion by title |
| 47 | Chan KH, Fried D. Selective Removal of Dental Composite using a Rapidly Scanned Carbon Dioxide Laser. Lasers in Dentistry Xvii. Proceedings of SPIE. 78842011. | Exclusion by title |
| 48 | Chan KH, Hirasuna K, Fried D. Rapid and selective removal of composite from tooth surfaces with a 9.3µm CO2 laser using spectral feedback. Lasers in Surgery and Medicine. 2011;43(8):824-32. | Exclusion by title |
| 49 | Chaushu S, Dykstein N, Ben-Bassat Y, Becker A. Periodontal status of impacted maxillary incisors uncovered by 2 different surgical techniques. J Oral Maxillofac Surg. 2009;67(1):120-4. | Exclusion by title |
| 50 | Chen P, Yu S, Zhu G. The psychosocial impacts of implantation on the dental aesthetics of missing anterior teeth patients. British Dental Journal. 2012;213(11). | Exclusion by title |
| 51 | Cholakova R, Chenchev I, Jordanova S, Oncheva D, Chenchev L. A case of compound maxillary odontoma and mandibular hypodontia. Journal of IMAB - Annual Proceeding (Scientific Papers). 2016;22(3):1217-20. | Exclusion by title |
| 52 | Chu CH, Zhang CF, Jin LJ. Treating a maxillary midline diastema in adult patients A general dentist's perspective. Journal of the American Dental Association. 2011;142(11):1258-64. | Exclusion by title |
| 53 | Chu FCS. Clinical considerations in managing severe tooth discoloration with porcelain veneers. Journal of the American Dental Association. 2009;140(4):442-6. | Exclusion by title |
| 54 | Clocheret K, Willems G, Carels C, Celis JP. Dynamic frictional behaviour of orthodontic archwires and brackets. Eur J Orthod 2004;26(2):163-70. | Exclusion by title |
| 55 | Contreras-Bulnes R, Scougall-Vilchis RJ, Rodríguez-Vilchis LE, Centeno-Pedraza C, Olea-Mejía OF, Alcántara-Galena MDCZ. Evaluation of self-etching adhesive and Er:YAG laser conditioning on the shear bond strength of orthodontic brackets. The Scientific World Journal. 2013;2013. | Exclusion by title |
| 56 | Cosyn J, Verelst K. An efficacy and safety analysis of a chlorhexidine chewing gum in young orthodontic patients. J Clin Periodontol. 2006;33(12):894-9. | Exclusion by title |
| 57 | Czochrowska EM, Stenvik A, Zachrisson BU. The esthetic outcome of autotransplanted premolars replacing maxillary incisors. Dental Traumatology. 2002;18(5):237-45. | Exclusion by title |
| 58 | Dai F, Li Y, Chen G, Chen S, Xu T. A novel method for prediction of dynamic smiling expressions after orthodontic treatment: a case report. Computer Methods in Biomechanics and Biomedical Engineering. 2016;19(3):340-6. | Exclusion by title |
| 59 | Davari A, Yassaei S, Karandish M, Zarghami F. In vitro evaluation of microleakage under ceramic and metal brackets bonded with LED and plasma arc curing. J Contemp Dent Pract. 2012;13(5):644-9. | Exclusion by title |
| 60 | de Carvalho V, de Carvalho C, de Carvalho A, Borges TGF, de Carvalho V, Santiago EFA. Statistical analysis of teeth autotransplantation in Portugal's region of Chaves. Acta Odontologica Scandinavica. 2014;72(3):179-86. | Exclusion by title |
| 61 | De Cicco V. Cerebro-afferent vessel and pupillary basal diameter variation induced by stomatognathic trigeminal proprioception: A case report. Journal of Medical Case Reports. 2012;6. | Exclusion by title |
| 62 | Demirci M, Tuncer S, Oztas E, Tekce N, Uysal O. A 4-year clinical evaluation of direct composite build-ups for space closure after orthodontic treatment. Clinical Oral Investigations. 2015;19(9):2187-99. | Exclusion by title |
| 63 | Diniz MB, Aranha AMF, Giro EMA. Reabilitação de dentes anteriores traumatizados pela técnica da colagem de fragmentos. J Health Sci Inst. 2008;26(3):366-71. | Exclusion by title |
| 64 | Domínguez-Mompell Micó R, De la Cruz Fernández C, Marcianes Moreno M, Morón Duelo R, García-Camba Varela P, Varela Morales M. Incisivos en pala: frecuencia en pacientes ortodóncicos de diversas etnias. Cient dent (Ed impr). 2014;11(1):15-20. | Exclusion by title |
| 65 | Dostálová T, Tauferová E, Teuberová Z, Seydlová M, Smutný V, Racek J, et al. Shape and size of dental arch: A five-year prospective study. Methods of Information in Medicine. 2006;45(2):191-4. | Exclusion by title |
| 66 | Dua D, Dua A. Reconstruction and intentional replantation of a maxillary central incisor with a complete vertical root fracture: A rare case report with three years follow up. Journal of Clinical and Diagnostic Research. 2015;9(9):ZD06-ZD9. | Exclusion by title |
| 67 | Dueled E, Gotfredsen K, Trab Damsgaard M, Hede B. Professional and patient-based evaluation of oral rehabilitation in patients with tooth agenesis. Clin Oral Implants Res. 2009;20(7):729-36. | Exclusion by title |
| 68 | Duque C, Negrini Tde C, Sacono NT, Spolidorio DM, de Souza Costa CA, Hebling J. Clinical and microbiological performance of resin-modified glass-ionomer liners after incomplete dentine caries removal. Clin Oral Investig. 2009;13(4):465-71. | Exclusion by title |
| 69 | Dursun E, Savard E, Vargas C, Loison-Robert L, Cherifi H, Bdeoui F, et al. Management of Amelogenesis Imperfecta: A 15-Year Case History of Two Siblings. Operative Dentistry. 2016;41(6):567-77. | Exclusion by title |
| 70 | Fanghänel J. Biomechanics and biomaterials in oral rehabilitation and dental treatment. Biomedizinische Technik. 2008;53(5):213-4. | Exclusion by title |
| 71 | Farrow ML, Newman SM, Oesterle LJ, Shellhart WC. Filled and unfilled restorative materials to reduce enamel decalcification during fixed-appliance orthodontic treatment. Am J Orthod Dentofacial Orthop. 2007;132(5):578.e1-6. | Exclusion by title |

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|---|---|---|
| 72 | Fernandes LMPdSR, Rodriguez MHH, Lascala CÂ. Dentinogênese imperfeita familiar: relato de caso. Rev odonto ciênc. 2008;23(2). | Exclusion by title |
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**Appendix 4**. Descriptive statistics of the re-analyzed provided data of Karamouzos et al.

| **Outcome** | **Teeth** | **Mean (SE)** | **95% CI** | **Range** |
|---|---|---|---|---|
| Overall ΔE | 416 | 2.80 (0.09) | 2.62, 2.98 | 0.58-6.08 |
| | | | | |
| **Outcome** | **Teeth (%)** | | | |
| Teeth with ΔE>3.7 | 54 (13.0%) | | | |
| | | | | |
| **Teeth with ΔE>3.7/ patient** | **Patients (%)** | | | |
| 0 | 5 (20.0%) | | | |
| 1 | 6 (24.0%) | | | |
| 2 | 5 (20.0%) | | | |
| 3 | 5 (20.0%) | | | |
| 4 | 3 (12%) | | | |
| 6 | 1 (4.0%) | | | |

CI, confidence interval; SE, standard error.

**Appendix 5**. Re-analysis of the provided data of Karamouzos et al: generalized linear regression analysis on the treatment-induced color change ($\Delta E$).

| | | Univariable | | | Multivariable | |
|---|---|---|---|---|---|---|
| **Category** | **Group** | **β (95% CI)** | **P** | | **β (95% CI)** | **P** |
| Adhesive | Light-cured | Referent | | | Referent | |
| | Chemically-cured | 0.41 (0.30,0.51) | <0.001 | | 0.41 (0.30,0.51) | <0.001 |
| | | | | | | |
| Tooth | Central incisor | 0.02 (-0.15,0.19) | 0.82 | | 0.02 (-0.15,0.19) | 0.82 |
| | Lateral incisor | 0.31 (0.12,0.51) | 0.001 | | 0.31 (0.12,0.51) | 0.001 |
| | Canine | Referent | | | Referent | |
| | 1st premolar | 0.30 (0.06,0.53) | 0.01 | | 0.30 (0.06,0.53) | 0.01 |
| | | | | | | |
| Jaw | Maxilla | -0.11 (-0.31,0.10) | 0.31 | | NT | |
| | Mandible | Referent | | | | |
| | | | | | | |
| Side | Right | -0.02 (-0.15,0.11) | 0.76 | | NT | |
| | Left | Referent | | | | |

β, unstandardized regression coefficient; CI, confidence interval; NT, not tested.

**Appendix 6**. Re-analysis of the provided data of Karamouzos et al: generalized binary regression analysis on the number of teeth with treatment-induced color changes that are clinically visible ($\Delta E \geq 3.7$).

| | | Univariable | | | Multivariable | |
|---|---|---|---|---|---|---|
| **Category** | **Group** | **RR (95% CI)** | **P** | | **RR (95% CI)** | **P** |
| Adhesive | Light-cured | Referent | | | Referent | |
| | Chemically-cured | 2.60 (1.58,4.27) | <0.001 | | 2.58 (1.58,4.23) | <0.001 |
| | | | | | | |
| Tooth | Central incisor | 1.86 (0.95,3.62) | 0.07 | | 1.87 (0.95,3.66) | 0.07 |
| | Lateral incisor | 3.00 (1.42,6.35) | 0.004 | | 2.97 (1.41,6.23) | 0.004 |
| | Canine | Referent | | | Referent | |
| | 1$^{st}$ premolar | 1.86 (0.76,4.55) | 0.18 | | 1.87 (0.76,4.58) | 0.17 |
| | | | | | | |
| Jaw | Maxilla | 0.93 (0.46,1.89) | 0.84 | | NT | |
| | Mandible | Referent | | | | |
| | | | | | | |
| Side | Right | 1.35 (0.85,2.15) | 0.21 | | NT | |
| | Left | Referent | | | | |

CI, confidence interval; RR, relative risk; NT, not tested.

**Appendix 7**. Further details on the present review.

**Author contributions**

RK, SNP, and TE conceived the idea. RK wrote the first draft of the protocol. RK, SNP, and TE revised the protocol. SNP performed the literature searches and extracted search hits. RK did screening by title, study selection by abstract and full-text, data extraction, and assessment of the risk of bias in duplicate, while SNP checked all procedures independently by replication and TE resolved any conflicts that arose. SNP handled communications with trialists and performed the statistical analysis. RK wrote the first draft of the manuscript. RK, SNP, and TE assisted in the interpretation of the results and revised the manuscript draft. SNP submitted the manuscript and is the guarantor and responsible for the accuracy of the data and for future updates of the review.

**Data sharing**

The full dataset from this study will be uploaded and will be freely available through Zenodo upon acceptance. The individual patient data provided by Dr. Karamouzos have not been uploaded and can be requested by Dr. Karamouzos himself.

**Post hoc changes to the protocol**

- Outcome selection: we had initially planned to include the overall color changes ΔE as primary outcome, the three segregated parameters (ΔL*, Δa*, and Δb*) as secondary outcomes, and subjective assessments of color as secondary outcome. Due to the small number of contributing studies and the fact that the ΔL*, Δa*, and Δb* are integrated in the ΔE, which is more clinically relevant, the three parameters ΔL*, Δa*, and Δb* were not included finally and we focused on the primary outcome. The secondary outcome of subjective color assessment was not reported from any included studies.
- Additional analysis: a sensitivity analysis was conducted post hoc to alleviate the extreme heterogeneity seen in a meta-analysis. This was planned to be conducted in cases of high heterogeneity.
- Analyses of reporting biases were planned in protocol, but could not be conducted as < 10 studies were finally included.
    - Several subgroup analyses were planned in protocol, but could not be conducted as < 5 studies were finally included.